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10/823,690	04/14/2004	Steven J. Soldin	31603-2055	5374

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EXAMINER	
MUI, CHRISTINE T	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/823,690	SOLDIN, STEVEN J.	
	Examiner	Art Unit	
	CHRISTINE T. MUI	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-36,39-53 and 55-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-36,39-53 and 55-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

1. The AMENDMENT TO THE ABSTACT submitted 22 May 2008 should have been submitted as a separate paper as required by 37 CFR 1.4(c). The paper has been entered. However, all future correspondence must comply with 37 CFR 1.4.

1. Applicant's arguments, see REMARKS, filed 22 May 2008, with respect to claims 1, 58, 60 and 62 have been fully considered and are persuasive. The objection of claims 1, 58, 60 and 62 has been withdrawn.

2. Applicant's arguments filed 22 May 2008 have been fully considered but they are not persuasive.

3. Applicant asserts that the reference DeBrabandere does not disclose the method for analysis of small samples of biological fluid is within 100 microliters or 700 microliters. Examiner believes that the volume of the sample tested is obvious in view of DeBrabandere. Applicant asserts that DeBrabandere avoids stating how much serum is used for testing but it appears to be somewhere between 0.6 mL and 1.5 mL. Examiner believes that it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the sample size so that it is 100 microliters to analyze an extremely small sample without having to use a larger sample and to modify the amount of sample tested, since it has been held that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum value by routine experimentation. *In re Aller, 220 F. 2d 454, 456, 105, USPQ 233, 235 (CCPA 1955).*

4. Applicant asserts that the reference Jonnson does not teach analysis of a thyroid hormone, but Jonnson does teach a method for the analysis performed on cortisol in saliva by liquid chromatography tandem mass spectrometry, using a Perkin-Elmer Series 200 liquid chromatography system with an autosampler couple to an API 3000 LC-MS-MS. Since the method of claim is in reference to testing a thyroid and steroid hormone, it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the thyroid testing to the same testing conditions as the steroid hormone so that one can simultaneously test both hormones to save time and money in analysis.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-8, 12-27, 58-59 and 60-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeBrabandere et al (herein referred "DeBrabandere").

8. Regarding claims 1-3, 6, 12-27, 58-59 and 63, the reference DeBrabandere discloses a method for the determination of thyroxine in serum. The method is based on isotope dilution-liquid chromatography/tandem mass spectrometry using electrospray for ionization, after flow injection of thyroxine into the system. The internal standard was used and sample pretreatment consisted of protein precipitation and a two step liquid/liquid extraction procedure, where HPLC was performed on a Hypersil BDS C-18 column with an eluent containing methanol/water/formic acid. Thyroxine and its isotopically labeled analogue were measured in the selected reaction monitoring mode in both the positive ion and negative ion mode. Mass spectrometry measurements were performed in the selected ion monitoring mode and then switched to the multiple reaction monitoring mode to obtain interference free ion chromatograms. Upon preparation of the standard solutions, approximately 3 mg of the thyroxine was used and dissolved in 10 mL of methanol with a few drops of HCl. During extraction of thyroxine from the serum sample an exact serum volume, corresponding to approximately 50 ng of thyroxine was pipetted into a conical 5 mL vial. To the vial was added 50 ng of the internal standard. Extraction was performed by allowing the mixture to equilibrate and 2 mL portion of acetone/30% HCl solution was added and mixed to deprotenize the sample. The mixture was centrifuged and cooled and then centrifuged again in a refrigerator and the supernant was transferred to another vial and its pH was adjusted with HCl. The measurement of the protocol was injected into the column such that three injections of the calibrators preceded and followed four serum samples to give an approximate isotope ratio of one (see pages 1099-1103). DeBrabandere does not

specifically disclose the sample volume to be tested, but it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the sample size so that it is 100 microliters to analyze an extremely small sample without having to use a larger sample and to modify the amount of sample tested, since it has been held that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum value by routine experimentation. *In re Aller, 220 F. 2d 454, 456, 105, USPQ 233, 235 (CCPA 1955).*

9. Regarding claims 4-5 and 7-8, the reference DeBrabandere discloses extracting thyroxine from serum (see abstract). It would have been obvious to one having ordinary skill in the art at the time the invention was made to extract thyroxine from another biological sample such as blood, plasma, urine or saliva as this is where the endocrine glands release thyroid hormones in the body.

10. Regarding claim 60-62, the reference DeBrabandere discloses the claimed invention except for all the reagents for deprotenating, separating and analyzing one or more thyroid hormones and instructions for using a mass spectrometer into a kit, but it would have been obvious to one having ordinary skill in the art at the time the invention was made to include and incorporate all necessary reagents, solutions, samples and instructions required for performing the mass spectrometry of thyroid hormones taught by DeBrabandere in a kit form as to making analyzing thyroid hormones an easy, accessible and convenient way to perform an analysis in a centralized location facilitating easy, efficient and effective analysis without having to have various reagents, solutions and samples all in different locations inhibiting efficient analysis.

11. Regarding claims 64-65, the reference DeBrabandere discloses the LC/MS/MS instrument used was a VG Quattro II mass spectrometer (see page 1100). It would have been obvious to one having ordinary skill in the art at the time the invention was made to use either an API 2000 or 3000, as mass spectrometers are instrument that measures the mass-to-change ration of ion in a sample and any of the mass spectrometer machines will perform this task. Furthermore, it is a matter of the experimenter's choice as to decide what mass spectrometer is to be used.

12. Claims 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeBrabandere as applied to claim 1 above, and further in view of USP 4,741,897 to Andrews et al.

13. Regarding claims 10-11, the reference DeBrabandere discloses the claimed invention except for using acetonitrile to deproteinate the thyroxine sample. DeBrabandere discloses using an exact serum volume, corresponding to approximately 50 ng of thyroxine, in a conical vial. Thereto, 50 ng of the internal standard was added and extraction was performed where sodium chloride was added and dissolved under vortexing and the mixture was left to equilibrate for 1 hour and then a mixture of actone/30% HCl solution was added and mixed to deprotenize the sample. Ethylacetate was added to the mixture to extract the thyroxine sample (see pages 1100-1001). Andrews discloses a method to extract thyroid hormones from biological fluids such as serum. Andrews discloses a method of extracting L-thyroxine from a mixture of L-thyroxine and histamine and DI and acetonitrile. The mixture was stirred until dissolved and to the mixture a solution of DSS in acetonitrile was added and the

resulting mixture was stirred overnight and stored until purification where a white precipitate was collected by centrifugation (see Example 4). It would have been obvious to one having ordinary skill in the art at the time the invention was made to use acetonitrile instead of a mixture of actone/30% HCl solution to deproteinize the thyroxine from the serum sample to ensure proper deproteinization and clean cleavage or extraction of thyroxine from the serum.

14. Claims 28-31, 34, 41-45 and 47-53 and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeBrabandere, and further in view of Draisci et al (herein referred "Draisci").

15. Regarding claims 28-31, 34, 41-45 and 47-53 and 55-57, the reference DeBrabandere discloses a method for the determination of thyroxine in serum. The method is based on isotope dilution-liquid chromatography/tandem mass spectrometry using electrospray for ionization, after flow injection of thyroxine into the system. The internal standard was used and sample pretreatment consisted of protein precipitation and a two step liquid/liquid extraction procedure, where HPLC was performed on a Hypersil BDS C-18 column with an eluent containing methanol/water/formic acid. Thyroxine and its isotopically labeled analogue were measured in the selected reaction monitoring mode in both the positive ion and negative ion mode. Mass spectrometry measurements were performed in the selected ion monitoring mode and then switched to the multiple reaction monitoring mode to obtain interference free ion chromatograms. Upon preparation of the standard solutions, approximately 3 mg of the thyroxine was used and dissolved in 10 mL of methanol with a few drops of HCl. During extraction of

thyroxine from the serum sample an exact serum volume, corresponding to approximately 50 ng of thyroxine was pipetted into a conical 5 mL vial. To the vial was added 50 ng of the internal standard. Extraction was performed by allowing the mixture to equilibrate and 2 mL portion of acetone/30% HCl solution was added and mixed to deprotenize the sample. The mixture was centrifuged and cooled and then centrifuged again and then placed in a refrigerator and then supernant was transferred to another vial and its pH was adjusted with HCl. The measurement of the protocol was injected into the column such that three injections of the calibrators preceded and followed four serum samples to give an approximate isotope ratio of one (see pages 1099-1103). DeBrabandere does not disclose analyzing steroid hormones using mass spectrometry. Draisci discloses a specific and sensitive method based on tandem mass spectrometry with on-line high performance liquid chromatography suing atmospheric pressure chemical ionization for the quantitation of anabolic hormone residues such as 17β-19nortestosterone, 17β-testerone and progesterone and the metabolites in bovine serum and urine. An internal standard of [$^2H_2$] 17β-testerone was used as an internal standard and the analytes were extracted from urine and serum by liquid-liquid extraction and purified by a C 18 solid phase extraction. Ionization was performed in the positive mode where only the protonated molecule was generated for each analyte and the served as the precursor ion for collision induced dissociation and two diagnostic product ions for each analyte were identified for the unambiguous hormone confirmation by selected reaction monitoring. A 2 mL serum sample was fortified with 4 ng of an internal standard and 15 mL of acetate buffer solution and the mixture was sonicated

with an ultrasonic bath for 5 minutes. The sample was purified by solid phase extraction using a C18 cartridge. The analytes were eluted with 4 mL of methanol and the solvent was removed under nitrogen stream and the residue was dissolved in 100 mL of methanol. The volume of the solution was injected into the LC-MS-MS system. Similarly, a 2 mL sample of urine was fortified with 10 ng of an internal standard and added with 20 μL of a crude enzyme solution of *Helix pomatia* and the mixture was incubated and extracted the same way the serum was extracted. The experiment could have also been performed in the selected ion monitoring mode to obtain the spectra with the maximum intensities of the protonated molecular ion of each analyte. DeBrabandere discloses a method for analyzing thyroid hormones in serum while Draisci discloses a method for analyzing steroid hormones in serum both under tandem mass spectrometry with high performance liquid chromatography, so therefore it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the analyzing techniques of steroids and hormones since the are both in a sample of serum and undergo the sample analyzing an characterization techniques and conducting this experiment would not only save experimentation time but looking at the issue of economics, would save on costs of performing the experiment only once rather than twice. DeBrabandere nor Draisci disclose a sample to be approximately 700 microliters, but it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the sample size so that it is approximately 700 microliters to analyze an extremely small sample without having to use a larger sample and to modify the amount of sample tested, since it has been held that where the

general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum value by routine experimentation. *In re Aller, 220 F. 2d 454, 456, 105, USPQ 233, 235 (CCPA 1955).*

16. Claims 32-33 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeBrabandere and Draisci as applied to claim 31 above.

17. Regarding claims 32-33 and 35-36, the reference DeBrabandere discloses extracting thyroxine from serum (see abstract). It would have been obvious to one having ordinary skill in the art at the time the invention was made to extract thyroxine from another biological sample such as blood, plasma, urine or saliva as this is where the endocrine glands release thyroid hormones in the body.

18. Claims 39-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeBrabandere and Draisci as applied to claim 28 above, and further in view of USP 4,741,897 to Andrews et al.

19. Regarding claims 39-40, the references DeBrabandere and Draisci discloses the claimed invention. DeBrabandere and Draisci disclose the claimed invention except for using acetonitrile to deproteinate the thyroxine and steroid samples. DeBrabandere discloses using an exact serum volume, corresponding to approximately 50 ng of thyroxine, in a conical vial. Thereto, 50 ng of the internal standard was added and extraction was performed where sodium chloride was added and dissolved under vortexing and the mixture left to equilibrate for 1 hour and then a mixture of actone/30% HCl solution was added and mixed to deprotenize the sample. Ethylacetate was added to the mixture to extract the thyroxine sample (see pages 1100-1001). Draisci discloses

2 mL serum samples are fortified with 4 mg of internal standard and 15 mL of acetate buffer solutions. The samples are then sonicated with an ultrasonic bath and the sample was purified by solid phase extraction using a C18 cartridge which was previously conditioned with 2.5 mL of methanol and 5 mL of water. The sample are then washed with 5 mL of ABS, water and a methanol-water mixture and the analytes were finally eluted with 4 mL of methanol and the solvent was removed under a nitrogen stream (see page 513). Andrews discloses a method to extract thyroid hormones from biological fluids such as serum. Andrews discloses a method of extracting L-thyroxine from a mixture of L-thyroxine and histamine and DI and acetonitrile. The mixture was stirred until dissolved and to the mixture a solution of DSS in acetonitrile was added and the resulting mixture was stirred overnight and stored until purification where a white precipitate was collected by centrifugation (see Example 4). It would have been obvious to one having ordinary skill in the art at the time the invention was made to use acetonitrile instead of a mixture of actone/30% HCl solution or an acetate buffer solution to deproteinize the thyroxine and steroids from the serum sample to ensure proper deproteinization and clean cleavage or extraction of thyroxine from the serum.

20. Claims 39-40 and 64-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeBrabandere and Draisci as applied to claim 28 above, and further in view of Jonsson et al (herein referred "Jonsson").

21. Regarding claims 39-40, the references DeBrabandere and Draisci discloses the claimed invention except for using acetonitrile to deproteinate the thyroxine and steroid samples. Jonsson disclose a method for the determination of cortisol in saliva by liquid

chromatography tandem mass spectrometry. The saliva was centrifuged; deuterium labeled cortisol was added to an internal standard the proteins were precipitated by acetonitrile. The supernant was dissolved in methanol and acified with acetic acid and analyzed by LC-MS-MS (see abstract). It would have been obvious to one having ordinary skill in the art at the time the invention was made to use acetonitrile instead of a mixture of actone/30% HCl solution or an acetate buffer solution to deproteinize the thyroxine and steroids from the serum sample to ensure proper deproteinization and clean cleavage or extraction of thyroxine from the serum. Furthermore, Jonnson does not specifically disclose performing the analysis on a thyroid hormone, but it would have been obvious to one having ordinary skill in the art at the time the invention was made to include the thyroid testing to the same testing conditions as the steroid hormone so that one can simultaneously test both hormones to save time and money in analysis.

22. Regarding claims 64-65, the references DeBrabandere and Draisci discloses the claimed invention except for using an API 2000 or an API 3000 as the mass spectrometer. Jonsson discloses the analysis performed on cortisol in saliva by liquid chromatography tandem mass spectrometry, used a Perkin-Elmer Series 200 liquid chromatography system with autosampler coupled to an API 3000 LC-MS-MS (see page 64). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use either an API 2000 or 3000, as mass spectrometers are instrument that measures the mass-to-change ration of ion in a sample and any of the mass spectrometer machines will perform this task.

Furthermore, it is a matter of the experimenter's choice as to decide what mass spectrometer is to be used.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINE T. MUI whose telephone number is (571)270-3243. The examiner can normally be reached on Monday-Thursday 7-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Walter Griffin can be reached on (571) 272-1447. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CTM

/Walter D. Griffin/
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